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EDITORIAL

The question has often been asked, "Why do the fifth and sixth year students not avail themselves of the clinical material at hand?" This is a legitimate question and really strikes at the very heart of our system of medical education. We shall attempt to answer this question. Unfortunately we are not thoroughly conversant with those systems which obtain in the other medical centres of Ontario, or Canada, so the following remarks will pertain to the system as followed in the University of Toronto.

In answer, then, to this question, we may consider several points. Firstly, the intern wears a white suit. This is a very real factor, for the student, in the eyes of the patient, is converted in the twinkling of an eye, from one who does not quite know his job and who is apt to make mistakes, to a doctor who knows his work and makes few errors. It is this change of attitude on the part of the patient that enables the intern to get, with little or no opposition, mayhap eagerness, a fairly good history. Also the intern obtains the story before the patient has had to recite it a dozen times or more. Both are interested because the story is new. And the in-

tern is keen to solve the diagnostic puzzle.

Secondly, the intern has probably seen the patient in the out-patients' department and so has been able to follow the progress of the illness, and after a stay in hospital, the patient is again seen on subsequent occasions at the out-door clinics. That is, there is a continuity of the study that the internist makes of a case which is not possible for the student.

Thirdly, there is an admirable system which obtains at the hospital. It is demanded that one's work be well done and up to date, following which, time may be taken off. Oddly enough, much time is not taken off. Chiefly because there is ample to do, but also there develops a spirit of honour which keeps the intern from shirking and he brands himself a rotter if he slacks on the job. In other words, there is a delightful feeling of freedom and a knowledge that one has only to walk out of the hospital doors to be free, for awhile, but it is this very feeling of freedom which holds the intern to his work. Not so, the student, for he has no honour about his work, for it is compulsory. Things must be done by such and such a day and hour regardless of his own interests. (We are not saying that this is not good for the student—that is another question).

Fourthly, the intern is with his work constantly, and has a responsibility thrust upon him, which he cannot dodge. The student, not being in a similar position, can hardly assume it to exist, no matter what a lively imagination he has.

Lastly, the spare hours of the intern, taken off, away from the ward are a relaxation. Let this be emphasized! It is time off with no thought of the ward or medicine or the university. It is a refreshing interlude that is of inestimable value in helping the intern to approach his work with renewed vigor. Compare that with the student. Always has he the spectre of examinations over his head, and though he may take a short respite from academic work, yet there is that licked-dog feeling that reminds one of the study and reading left in abeyance. The student's spare time is not a rest. It is merely an interlude of mental unrest till the flesh is goaded back to the active contemplation of that which has never really been completely forgotten, even for a short space of time.

This is the question answered. We are not bitter about the situation, but rather we interest ourselves in such problems with a view to understanding the difficulties experienced in organizing a medical course. That many Sixth Year students spend some time in the wards as interns living in the hospital, does seem a step in the right direction. Let us hope that that is the thin edge of the wedge which will eventually broaden out to include all Sixth Year men, and in time all Fifth and even Fourth Year men. That, we agree, is an deal, but an ideal to be striven for, both in the interests of the students and the profession.

We comment upon this topic because we feel that we are expressing student opinion by and large, especially so in regard to the favour which the student body views these student-internships during the academic year.

PREPARATION AND PROPERTIES OF THE LIVER PRINCIPLE EFFECTIVE IN PERNICIOUS ANAEMIA*

By E. W. McHENRY, M.A., Ph.D.
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Pernicious anaemia is a type of anaemia characterized usually by the presence of large, red blood cells and the ratio of haemoglobin to the number of red blood cells is greater than normal, although both are reduced. Separate manifestations of the disease are: abnormalities of the alimentary tract such as sore tongue and achlorhydria, and lesions of the central nervous system.

The first report of a case of pernicious anaemia was published by Combe of Edinburgh in 1822. The classical description by Addison, of the anaemia which so often bears his name, was given in 1855. No appreciable advance was made in the treatment of the condition until 1920. The lack of progress evidenced through this period of 100 years was due to theories of aetiology which now seem untenable. The change in thought which has resulted from the discovery of an efficient therapy may be illustrated by quotations from three reviews.

1. Muelengracht (Copenhagen), 1925. "The character of the disease has led to the following conclusions: It seems certain that we have to deal with a general intoxication, which in the later stages fatally affects the blood, and the blood forming organs . . . What causes are responsible for this intoxication, we do not know, but they seem to be connected in some way with the digestive tract."

2. Cornell, 1927. "Pernicious anaemia appears to be a superstructure of blood system and nervous changes superimposed upon an unknown, but characteristic, fluctuant foundation. Of this foundation we know nothing, but conceive of achlorhydria as its constant and only obvious expression. The widespread tissue involvement found, and the peculiar mass of biochemical changes suggest that this fundamental process is a disturbance of metabolism."

3. Lord Dawson, 1928. "Three possible links can be traced in the chair of aetiology: Achlorhydria, abnormal flora in the upper half of the alimentary tract, and the absence or insufficiency of a specific function of the liver."

In September, 1920, Whipple, Hooper and Robscheit from the University of California, published a series of four papers upon the influence of diet upon blood regeneration in simple anaemia. The key-note of the series and of subsequent work was given in the second sentence of the first paper: "It will be shown that the curve of haemoglobin regeneration can be influenced at will by various diet factors." Anaemia in dogs was produced by removal on two successive days of amounts of blood each equal to one-fourth of the calculated total blood volume. The animals were then given trial diets and changes in the blood picture studied. In the fourth paper it was reported that cooked liver was very efficient in bringing about a rapid blood regeneration. A watery liver extract also was found to exert a beneficial effect.

It is interesting to consider a significant paragraph from Whipple's Harvey Society Lecture of January 7, 1922. "Our conception of pernicious anaemia is that there is a scarcity of stroma building material or a decrease of the stroma forming cells of the mar-

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*Presented at a meeting of the Toronto Physiological Society, February 25, 1935.

row which limits the output of red cell framework. There is plenty of pigment material (an excess in fact) as evidenced by the high colour index."

Gibson and Howard of Iowa City appear to have been the first to utilize this information in clinical work. They reported in 1923 a series of 11 cases of pernicious anaemia treated satisfactorily with a diet containing liver. Nine years later these authors gave a history of three of the cases for the intervening period.

Whipple and his associates published in 1925 a further series of papers on blood regeneration in the dog. Changes in technique were adopted, the details of which need not concern us. It was stated with considerable emphasis that liver feeding was highly satisfactory and clinicians were urged to try it in the treatment of pernicious anaemia.

Whipple's advice was promptly heeded. Minot and Murphy reported in August, 1926, on 45 cases which had been given a diet rich in liver for about eight months. The diet recommended by these authors was not one necessarily high in liver, but rather one furnishing a large amount of complete proteins and low in fat.

At this time Koessler of Chicago was advocating the treatment of pernicious anaemia by feeding a diet rich in vitamin A, supplied, as he said, to counteract the bacterial toxin held to be responsible for the disease.

By September, 1927, Minot and Murphy were convinced that the effectiveness of their diet was due to the liver which it contained. Proceeding on the asumption that the liver contained an anti-anaemia substance, simple extracts were prepared, and found to be active. In 1928 they stated that the anaemia of pernicious anaemia is primarily dependent upon the failure of the primitive cells in the bone marrow to differentiate toward mature erythrocytes. The active substance in liver stimulated the bone marrow. This view was reiterated by Whipple in a review published in the same year (1928).

In the preparation and fractionation of liver extracts Cohn aided Minot and Murphy. In the first joint publication, July, 1927, a simple system of fractionation was employed which yielded two active fractions, D and G. Two parts of this procedure are noteworthy. Proteins were removed by heating a mixture at pH5 to 70°C. An active fraction was secured by alcohol precipitation.

Following the publication of this method, preparation of the two fractions, D and G, was begun in the Connaught Laboratories by Doctors Best and Scott.

Early in 1928 Cohn, Minot and associates, described a modified procedure for preparing active fractions. One advance there described has since been found helpful. The active material is soluble in 70% alcohol and insoluble in 95% alcohol. Several properties of the active principle were noted in this paper. Active fractions were prepared free from iron, protein, carbohydrates and lipoids. The active principle was not precipitated by basic lead acetate, but was precipitated by phosphotungstic acid. It was thought to be either a nitrogenous base or a polypeptide.

A procedure based largely on this paper was employed in 1928, when large-scale preparation of liver extract was begun in the Connaught Laboratories. For some months extract was distributed in solution in eight ounce bottles. Obvious problems of sterility caused a change to a more convenient form and since 1929 the laboratories have prepared liver extract in the form of a powder. For five years a standard procedure which is known to produce an active extract has been followed. Efforts have been made to adhere rigidly to this process, but to make such mechanical changes as would promote ease of handling and economy. A general outline is as follows: Fresh beef liver is minced and extracted with wa-

ter acidified with sulphuric acid to pH5. After one hour stirring the mixture is heated to 70° and filtered through large bags. The residue is re-extracted with cold water. The combined extracts are concentrated in vacuo to about one-eighth the original volume. Two volumes of 90% alcohol are added, giving a concentration of about 55% alcohol. An inactive precipitate is removed. The active filtrate from a week's production is concentrated to a thick syrup and poured into absolute alcohol, enough being used to ensure a final alcohol concentration of 95%. The resultant precipitate is dried in a vacuum oven and ground to a fine powder. This powder is highly hygroscopic and the grinding is carried out in a special, dehumidified cabinet. Average yields over a period of three years have given two per cent. of the initial weight of liver in final powder form. This does not mean that 1 lb. of powder contains the activity of 50 lbs. of liver. There is appreciable loss during precipitation and the final product contains 50 - 60% of the active substance contained in the original liver.

In 1930 Gänsslen of Tubingen reported successful treatment of 40 cases of pernicious anaemia by parenteral administration of a highly active liver extract. Unfortunately no details were furnished, nor have yet been given, as to the mode of preparation. A year later Castle and Taylor discussed the intravenous use of a crude solution of Cohn's fraction G. This contained depressor substances and intravenous administration caused some untoward effects. Because of these effects, Strauss, Taylor and Castle, suggested the use of intramuscular injection, which gave responses as promptly as intravenous treatment. They employed a sterilized, buffered solution of liver extract powder.

Preparation of solution for intramuscular injection was begun in the Connaught Laboratories in 1931 by the procedure employed by Strauss, Taylor and Castle. Clinical trials during a period of over a year showed that this therapy was advantageous and general distribution was undertaken in 1933. At first solutions were such that one c.c. contained extract prepared from 5 grams. Results secured by Dr. Farquharson indicated that solutions having double this concentration were advantageous and the product now being distributed is such that one c.c. contains the material extracted from 10 grams of liver.

The method by which the solutions are prepared is briefly as follows: Extract powder of the calculated weight is mixed with water and the mixture heated to 70°C. with continuous agitation. It is then cooled and the pH buffered at 7 by the addition of sodium phosphate and sodium hydroxide. It is then stored in the cold for several days. During this time a precipitate accumulates. This is removed and the solution, to which has been added 0.3% tricresol, is sterilized by passage through a Seitz filter.

Extensive clinical trials here and in other places have shown that the treatment of pernicious anaemia by intramuscular injection has several advantages. Injections are generally painless and without untoward reactions. Nausea is not produced nor augmented as in the case of oral treatment. Prompt responses are secured.

One aspect of intramuscular treatment is worth emphasis. It is probably the most economical method of handling pernicious anaemia. A given weight of liver extract is at least 50 times as active given parenterally as when administered by mouth.

The solution prepared for intramuscular use contains depressor substances, probably histamine and choline. An average extract has a depressor effect equivalent to that caused by 2 mg. per cent. histamine. Efforts to remove these depressor substances without also removing the active principle have not been fruitful. Since Whipple had shown that kidney is about as useful as liver and since kid-

ney is particularly free from depressor substances a solution was prepared from beef kidney. This was tried on patients and had unexpected toxic effects which rendered further use impossible.

Whipple reported last year that horse liver was almost twice as potent as beef liver. We have prepared for clinical trial two lots of solution from horse liver. It is interesting that, with the same process, horse liver yields one-half the weight of extract that is secured from beef liver. Moreover, horse liver extract is remarkably low in depressor effects. However, preliminary results indicate that horse liver extract is no more potent than is beef liver extract. This confirms a recent paper by Conner.

It should be pointed out that the solutions prepared for intramuscular use are free from protein. Attempts to produce anaphylaxis in guinea-pigs with them were unsuccessful. Each lot is tested on three species of animals before release. Injections in rabbits and mice are done and the animals observed for some days to ensure lack of toxicity. By customary methods the extracts are assayed for depressor properties in cats. Reference will be made later to precautions regarding anti-anaemic potency.

In 1927 Castle of Harvard formulated a hypothesis which has had a profound effect on considerations of the aetiology of pernicious anaemia. A characteristic symptom in this disease is gastric achylia. The stomach is primarily designed for peptic digestion of protein and Castle postulated that persons suffering from pernicious anaemia are unable so to digest proteins as to liberate a substance which is necessary for red blood cell formation. This substance is contained in liver. Acting on this assumption, Castle had normal individuals eat minced beef muscle, itself not haemopoietic. After 45 minutes the stomach contents were removed and fed to pernicious anaemia cases. A definite reticulocyte response, characteristic of liver therapy, was secured. Similar results were obtained when beef muscle was incubated with normal gastric juice in vitro. No such effect was found when the gastric juice was heated before use. Moreover, the result could not be secured if saliva or duodenal juice was employed in place of gastric juice. The production of a haemopoietic substance from beef muscle is consequently due to the action of a thermo-labile, enzyme-like substance in stomach contents.

It seemed logical for Castle, then, to formulate an explanation of these results. Two factors were postulated: (a) an intrinsic factor; (b) an extrinsic factor. The intrinsic factor is secreted by active normal gastric mucosa, and is not present in detectable amounts in the gastric intestinal tract of patients with pernicious anaemia. Since Castle found that the extrinsic factor was furnished by proteins precipitated from beef muscle at pH 6 he assumed that the extrinsic factor was protein or of a closely related nature. The reaction between the two factors could take place at neutrality and in the absence of pepsin and rennin. The intrinsic factor is, then, not hydrochloric acid, pepsin or rennin. While washed beef muscle protein furnishes the extrinsic factor, purified casein and wheat gluten do not. Autolysed yeast alone (which is a good source of vitamin B_2) is ineffective in pernicious anaemia; after incubation with normal gastric juice it is haemopoietic. This, coupled with other parallelisms between the extrinsic factor and vitamin B_2 led Castle to believe that these two substances were identical.

It has been found by several workers that commercial liver extracts, known to be active, do not contain vitamin B_2. Moreover, vitamin B_2 preparations are ineffective in pernicious anaemia. This is held to be a blow at Castle's assumption that the vitamin is the extrinsic factor. Such is not the case since it is necessary that the extrinsic factor and the intrinsic

factor react together to form the haemopoietic substance. Better proof has been furnished, however, by incubating egg white, a good source of B_2, with normal gastric juice. The resultant mixture was found by Wills and Naish and by others not to be haemopoietic. It is now generally believed that vitamin B_2 is not the extrinsic factor.

In a series of papers Klein and Wilkinson of Manchester have described an enzyme secured from gastric tissues, which seems to be identical with Castle's intrinsic factor. They have given to this enzyme the unwarranted name, "haemopoietin." This substance is entirely distinct from the liver principle. Extraction procedures which yield active products from liver yield no activity when applied to stomach. Like the intrinsic factor haemopoietin is thermolabile while liver principle is thermostable. An active solution of haemopoietin can be secured by pressing out juice from minced stomach tissue. The haemopoietic substance formed by incubating beef muscle with gastric juice is strikingly similar to the liver active principle. Wilkinson and Klein picture the relationship of the various factors as follows:

Enzyme (Haemopoietin) (Intrinsic Factor) Stomach.	Substrate (extrinsic factor) unknown constituent of beef muscle Food.	End Product Haemopoietic Substance (Liver Principle) Formed in Stomach— Stored in Liver, etc.

Prompted by the hypothesis advanced by Castle, Sturgis and Isaacs of Ann Arbor in 1929 used hog stomach tissue in treating cases of pernicious anaemia. The tissue was simply minced and dried, or defatted with petroleum ether and dried. Satisfactory results were secured and Parke-Davis have since marketed "Ventriculin," a desiccated hog stomach powder.

Conner of the Mayo Clinic reported in 1931 on the activity of various sections of stomach. Fed separately, mucosa, residue after removal of mucosa, and whole gastric wall gave equivalent results. Tissue from the fundus or the pylorus was of equal value. This has been denied recently by Muelengracht who found that preparations carefully made by the fundus section of hog stomach were entirely inactive.

It is most likely that stomach preparations are active, not only because they contain the intrinsic factor but also the extrinsic substance. Interaction of the two during the course of preparation or during digestion, yields the haemopoietic factor which is found in liver.

Morris, Schiff and associates have described the use of gastric juice which has been concentrated by vacuum distillation. Normal, unconcentrated juice is not haemopoietic, while the concentrated juice is active. Without any great necessity the authors stated that this concentrated juice contained a new haemopoietic substance, a hormone secreted by the stomach, and named by them "Addisin." Hermer, Fouts and Zerfas have recently (1934) furnished an explanation of this effect. Gastric juice normally contains both the intrinsic and the extrinsic factors. During concentration by distillation in vacuo the temperature is favourable to the reaction between the two factors to produce the substance normally found in the liver and which is identical with the so-called Addisin.

Two series of reports have appeared regarding the possibility of increasing the amount of active principle secured from liver. Members of the research staff of the Eli Lilly Company have claimed that the potency of liver extract powder can be increased by incubating it with stomach tissue. The product thus prepared has been named "Extralin" and is said to be three to four times as active as before incuba-

tion. It is curious that when patients are given this preparation a reticulocyte response is secured but the red blood cell count rises slowly and the haemoglobin remains low. It is suggested that iron should be given concurrently. A recent communication by Conner states that Extralin has about the same potency as ordinary liver extract.

Herron and McEllroy of Pittsburg have described a method for prolonged autolysis of liver. The crude filtrate is said to be highly active and this procedure has been patented. In the case of this preparation and also in the case of Extralin it seems impossible to carry the increased potency through any purification procedure, even the simple one ordinarily used for liver extract. Some half dozen different autolytic procedures have been tried in these laboratories. Clinical tests by Dr. Farquharson and Dr. Mills of Montreal have shown us that no increase in potency resulted.

Reference has been made to the finding by Robscheit-Robbins and Whipple that horse liver is almost twice as potent as is beef liver. These authors have done quantitative studies on liver from a number of species. Several groups of investigators, particularly Wilkinson and Klein, have shown that normal human liver contains ample amounts of the active substance, that it is absent from untreated cases of pernicious anaemia, and present in the livers of cases adequately treated with liver extract. The liver is regarded as a storehouse for the anti-anaemia factor produced in the stomach by the action of the instrinsic factor upon the extrinsic substance. The active principle appears in the liver at least two months before birth (Goldhamer, Isaacs and Sturgis).

A great deal of work has been done to ascertain the nature of the liver principle. Reference has been made to attempts by Cohn to secure highly purified fractions. The substance is not precipitated by basic lead acetate but is brought down by phosphotungstic acid. Cohn was convinced that the factor was a nitrogenous base. West of New York with several associates prepared several active fractions and crystals which were at first thought to be potent, but later found to be inactive. The crystalline compound was a peptide containing hydroxy-glutamic acid and hydroxy-proline. Both Cohn and West obtained highly active fractions but to secure them enormous quantities of liver were employed. The amount of one of West's fractions required to give a reticulcoyte response was that prepared from 40 kg. liver. It is obvious that losses during purification were very great.

More recently Felix and Fruhwein in Germany have described a new fractionation procedure. From an aqueous extract of liver, protein is precipitated with tannic acid. The active principle is precipitated by means of mercuric sulphate in the presence of alcohol and ether. The active fraction contained 7% nitrogen but no peptides. It was biuret negative. Considering that so little is known regarding this substance we may recall with interest the sentence with which Cohn concluded a paper at Chicago in 1930: "Crystallization and identification of the active principle remain to be accomplished."

The unfortunate lack of progress in the elucidation of the nature of the liver principle is due, not to any lack of interest, but to the lack of a convenient assay method. At present only one method is available, testing fractions on human cases of pernicious anaemia. Available cases, suitable for test purposes, are few in number. It would be possible to carry out in a week purification studies, testing for which would occupy months as conditions stand.

A number of attempts have been made to devise a method of assay on animals. I shall briefly describe several of these.

It is well known that haemolysis and resultant anaemia may be produced

in rabbits by injections of B. Welchii toxin. Clark, and others, have claimed that animals thus treated will respond to treatment with active liver extract. Draper and Barach, and Goldwater, Connery and Heimann have shown that this anaemia is evanescent, the animals blood soon returning to normal without treatment. Moreover, the anaemia has no resemblance to pernicious anaemia in humans.

Vaughan reported in 1930 that the bone-marrow of healthy, grain-fed pigeons, was similar histologically to the bone marrow of cases of pernicious anaemia. She found that active liver extracts caused an increase in the reticulocytes of the circulating blood. This has been confirmed by Edmunds, Brueckner and Fritzell. Vaughan had stated that the reticulocyte count of normal, untreated pigeons varied considerably. Heimann, Connery and Goldwater found the fluctuation to be so great as to preclude the possibility of using any change as an indication of activity of liver extract. Moreover, extracts which they had demonstrated to be active in humans were without effect on pigeons.

McGowan has used two methods which he claimed to be useful in testing liver extract. Hens frequently suffer from anaemia resulting from infestation with an intestinal parasite (Davainea proglottima). Such birds are said to respond to liver extract. The second method was one in which pigs suffering from iron deficiency and consequent anaemia were thought to respond to liver treatment. Other workers have not placed great reliance on either procedure.

In their recent fractionation work Felix and Fruhwein have employed three methods of testing: (1) On cases of pernicious anaemia. (2) On normal men. These workers state that liver extracts cause a reticulcocyte rise in normal persons. This is at variance with several other reports. (3) Production of met-haemoglobin from haemoglobin in vitro. You will recall that methaemoglobin differs from haemoglobin in having the iron in the ferric state instead of the ferrous. This procedure was introduced by Dusberg and Kroll. Haemoglobin solutions prepared from pigs' blood are incubated with varying amounts of liver extract. Oxygen combining capacity determinations are used to ascertain the amount of haemoglobin which has been transformed to methaemaglobin. In correspondence, McFarlane of Edmonton has furnished me with results secured by this procedure and these are not in agreement with clinical findings.

Several speculations may be offered as to possible methods of animal assay. If Castle's extrinsic-intrinsic factor theory is correct it should be possible to produce anaemia, analogous to pernicious anaemia, in animals by deprivation of either or both factors. It is well known that anaemias may be produced in animals by dietary means but generally these are experiments on iron deficiency. It should be possible to devise a diet containing all essential constituents except the extrinsic factor. As a matter of fact Koessler and associates in their first report on the advisability of treating pernicious anaemia with vitamin A diets described the production of anaemia in rats by the use of a diet low in vitamin A. Examination of this diet shows that it was also deficient in the extrinsic factor. Such experiments might bear repetition. Several attempts have been made to eliminate the intrinsic factor by gastrectomy. Ivy and associates have shown that dogs and pigs do not develop pernicious anaemia after removal of the stomach. Maisson and associates have found that rats after gastrectomy do develop anaemia, but failed to report as to the type.

The most valuable contribution which could be made to this subject is a development of a satisfactory means of assay on animals. Following such developments rapid progress could be made on the chemistry of the active principle.

PATHOLOGY AND CLINICAL SIGNS OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

By J. D. HAMILTON, '35.

Subacute combined degeneration of the spinal cord is a disease most common in the second half of adult life, of which the onset is usually insidious and the course progressive to fatal termination. The advent of liver therapy has, however, changed the course and prognosis. The typical pathological lesion is a patchy degeneration of the white matter of the spinal cord, and the clinical picture one of subjective and objective sensations, alteration in deep reflexes, and change in muscle tone. The condition is accompanied by anaemia of Addisonian type in all cases sooner or later, except some of those of short duration.

Pathology.

In the majority of untreated cases the cord at autopsy appears larger than normal, and may or may not show gross lesions, depending on the duration. Some show no visible changes, other untreated cases of long standing appear shrunken, with antero-posterior flattening. The gross lesions which are sometimes seen consist of patches of softening which appear darker and more translucent than normal. Sometimes softer areas can be found but not seen. No gross changes in meninges are seen.

Microscopically the lesions are found to affect, primarily, the white matter. The area most affected is the mid-dorsal. The degeneration is most intense in this region, affecting the dorsal columns first and soon afterward the lateral columns. As the condition progresses spots of degeneration appear on either side of the antero-median fissure, and in the antero-lateral columns. These degenerated areas progress and coalesce, reach the surface of the cord and eventually involve the whole of the white matter with the exception of a small ring of internuncial fibres immediately adjacent to the gray matter. The poorer blood supply of the mid-dorsal region is thought to be the cause of primary involvement in this area. At the same time the lumbar and cervical segments are affected next in severity, the lower lumbar and sacral and upper cervical less. On going up, the degeneration tends to be limited to the posterior columns—the columns of Gall more than Burdach—and the dorsal and ventral cerebellar tracts, with scattered patches of degeneration in the direct pyramidal tracts and neighboring ground bundles. Destructive lesions are found as far up as the lower border of the pons. The upper pons and internal capsule are only rarely, if ever, involved.

Below the mid dorsal region the degeneration may be limited to patchy lesions of the pyramidal tracts and posterior columns, with less involvement, if any of the anterior columns. In the sacral region, pyramidal tracts only may be involved. Lissauer's Tract and the apex of the posterior horn may be entirely free. In many cases they do show involvement.

The structure first involved is the myelin sheath. Swelling occurs, followed by the appearance of irregularities, beading and finally breaking up into lipoid droplets. Secondarily the axis cylinders show changes first with slight swelling, then vacuolization, fragmentation and dissolution. Some axones may be preserved, with remnants of myelin in the form of minute globules. This destruction of myelin

eventually results in complete destruction of the axis cylinders. The fragmented myelin and axones are taken up by various gliogenous formations and phagocytes.

In contradistinction to the regressive changes seen in the nerve fibres, changes in the glia are of a phagocytic and proliferative nature. Scattered throughout the degenerated area numerous round cells can be seen. They are seen in especially large numbers about the adventitial coat of small and medium-sized blood vessels, where they may form a cuff several cell layers deep. Their size varies from that of a large mononuclear to less than a small lymphocyte, and they may be honeycombed, contain nothing but fat, or containing a large empty space in which are found fragments of myelin or axone. The origin of these cells is thought to be mainly the microglia and possibly also from adventitia and large mononuclears. Active mitosis of these cells has been seen. They are migratory, and on ingesting the lipoid and other products of degeneration, emigrate towards the adventitial space of a nearby blood vessel. With the injection of pigment into the perivascular spaces these compound granular corpuscles, or gitter cells, migrate back to the area of degeneration—that is they act as small transports.

Side by side with the production of gitter cells, there is a proliferative and phagocytic activity on the part of the glial cells. There are also more complicated and larger gliogenous formations—consisting of a number of chambers forming a net work containing remnants of myelin, axones, or fat globules. These are called myelophages, and may blend to form syncytial giant myelophages, with several nuclei. The function of myelophages is to break up and remove nerve remnants—that is to break them up into fat which is taken up by the granular cells. Giant glial cells with 1, 2, or 3 nuclei are found where regressive tissue changes are about complete. They are found near the blood vessels, and send processes to the adventitia. There is no true gliosis or scar formation in untreated cases of subacute combined degeneration, the proliferative changes seen having mainly to do with phagocytosis of the degenerated axones and myelin. The result of formation of giant glial cells, myelophages and other gliogenous elements, is the so-called status spongiosus which is a loose meshed incomplete replacement bearing fat laden phagocytes. In very long-standing lesions some shrinkage may occur.

Changes may take place in the cells of the gray matter with those of the anterior and posterior horns showing fatty changes and shrinking with slight chromatolysis, and excessive pigmentation. The lateral horns and dorsal ganglia show degenerative changes in some cases, which may help to explain various visceral and vascular symptoms. Elesewhere, extensive myelin degeneration results in lacunae filled with products of degeneration or clusters of phagocytes, instead of glial scar, but in the lateral horn zone glial reaction seems more complete and intense and may form a fairly dense mat.

Blood vessels do not show any characteristic changes with the exception of perivascular cuffing with compound granular corpuscles in the adventitial spaces of small and medium-sized blood vessels. In some there is a prolferation of adventitial connective tissue and thickening of adventitia. No well-defined changes in the adventitia, media or intima have been found. Multiple minute haemorrhages have been described but are not usual. The membranes do not show any characteristic changes. The dorsal roots sometimes show vascular swelling of the myelin sheaths, with loss of nerve fibres. The same lesions which are found in the cord are also found in the brain. Gross changes are not evident, but microscopically scattered foci of degeneration may be seen throughout the subcortical area. These lesions show degeneration of nerve fibres, with gliogenous

formations, gitter cells, and amyloid bodies. The white matter is much less affected. The foci of degeneration may or may not be about a blood vessel.

Specific changes may have been observed in peripheral nerves, but they are only found in a small percentage of cases. Swelling of the myelin sheaths, with irregularities, beading, vacuolization and demyelination have been observed. Here Schwann's cells remove the débris. However, no significant changes have been found in the peripheral nerves in autopsy material obtained at the Toronto General Hospital and even biopsy on a peripheral nerve in a patient with severe S.C.D. revealed no significant change.

Muscles show a decrease in number of fibres, thinning, and an increase in sarcolemma neuclei. The bone marrow in every case of subacute combined degeneration of the cord is hyperplastic. The gastro-intestinal tract shows the same findings as in pernicious anaemia. Other post-mortem findings depend on the degree of pernicious anaemia present.

Clinical Manifestations.

In a large majority of cases the signs and symptoms appear insidiously and without any exciting cause. Occasionally the onset is more rapid and may be preceded by severe gastro-intestinal symptoms such as vomiting, diarrhoea, jaundice, malaise, headache and pyrexia. At the Toronto General Hospital Dr. Hyland has found that symptoms characteristic of anaemia were prominent at the onset, and preceded the development of symptoms referable to the central nervous system, for varying periods of time in about two-thirds of the cases. In the remaining third nervous symptoms were the first indication of the disease.

The earliest symptoms complained of are subjective sensations and are present in every case. They are usually confined to the periphery of the limbs,—that is the fingers and toes,—but commonly extend to the trunk. Occasonally they may occur on the trunk, buttocks, perineum, neck, or back of the head. A unilateral distribution is not uncommon. By far the commonest forms for the paraesthesiae to take are numbness and tingling, although freezing, burning, stinging, or pricking in the limbs may occur, either alone or associated with numbness and tingling. Girdle pains are uncommon. These paraesthesiae may appear and disappear before cord changes can be demonstrated. They may also be absent in cases showing profound posterolateral sclerosis at autopsy. Almost all cases of pernicious anaemia without subacute combined degeneration of the cord show paraesthesiae at some period in their course. They are most often confined to the extremities and take the form of numbness and tingling only, and are very rarely associated with any impairment of sensation. The distribution of the paraesthesiae is segmental and not glove and stocking. This has been proven by very careful examination at the Toronto General Hospital, which revealed the absence of other signs of peripheral neuritis and hence make it an improbable cause of the disturbance. In long standing paraesthesiae, pronounced reddening of palms, fingers and toes may occur. This suggests some relation with the sympathetic nervous system. Involvement of the lateral horn of gray matter in the degenerative lesions has been referred to elsewhere in this paper. The cases at the Toronto General Hospital, with paraesthesiae of the upper limbs, showed a true Raynaud's syndrome in the fingers, which developed when they were suffering from pernicious anaemia.

Sensory loss or impairment is early. Loss or impairment of vibration sense is one of the earliest and commonest findings and is the most valuable sign in recording the onset or presence of a predisposition to subacute combined degeneration in cases of pernicious anaemia. It is first lost or diminished

in the toes or ankles and approaches normal as the limb is ascended, but is not uncommonly lost up to and including the anterior superior spines. Impairment in the upper extremity is relatively rare and only seen in very advanced cases. Joint sense and muscle sense and sense of position are commonly impaired in the lower extremities, where it is the rule to find maximum impairment in the distal parts. Defective joint sense in the upper extremities is late in appearance and always maximum in the fingers. When present it is always associated with some impairment of recognition of size and shape of objects placed in the hands. Actual stereo-anaesthesia is not common, it may be unilateral, and although recognition of texture is impaired, it is less affected than the ability to recognize size and shape.

Disturbances of gait and co-ordination are common. In some cases they must be regarded as possible manifestations of weakness as well as spasticity and loss of deep sensibility. Ataxia is seen in the majority of cases, although in addition there may be evidence of pyramidal tract disease in the lower limbs, as well as the impaired joint sense which determines the ataxia. The minority show a spastic ataxia form of gait while pure spastic gait is rare.

Superficial sensation is frequently impaired. The form the impairment takes is variable, but usually is such that it suggests a lesion of the spinal cord or posterior nerve roots rather than peripheral nerves. Occasionally impairment over back and thorax is noted, but the most usual impairment is in the extremities and is of varying degree. The distal parts are most affected as a rule, not in glove and sticking manner, but segmental in character. In general three main types of impairment are found, the three types differing only in degree depending on the severity of the lesions. The commonest variety is in the form of small patchy areas on the lower limbs and occasionally on the trunk. In such areas all forms of superficial sensation may be impaired, but commonly there is dissociation in degree at least. Pain and temperature are usually most affected and temperature less than pain, whereas light touch is involved very little. As the impairment spreads, pain is usually involved before temperature and touch. Occasionally touch is equally or more involved than the other two. As the condition progresses it shows a segmental distribution of impairment which may involve the trunk where it may show the same type of involvement as the limbs. Occasionally the most distal parts of the limbs show the most involvement with a tendency to lessen proximally. However, a variation in degree of disturbance in segmental areas is commonly found. Another type of sensory disturbance may be found in which the impairment terminates in a segmental level on the trunk: the level and degree may be different on the two sides. In later stages the patient may become anaesthetic up to the cervical region before death supervenes.

Signs of involvement of the pyramidal tract usually follow the appearance of subjective sensations, but may occasionally precede them. Paraplegic signs develop, either insidiously or sometimes rapidly. The patient first notices that the legs are easily tired and that he drags his feet in walking. Slight rigidity of the lower extremities with weakness especially of dorsiflexors of ankles and toes will be found, with increase of knee and ankle jerks, foot clonus, a tendency to pes cavus and Babinski response. The defects of co-ordination are shown by loss of sense of position and passive movement and ataxy of movement and Romberg's sign. Some cases form an exception in that the clinical picture may be one of ataxy with flaccid weakness throughout, with diminished or absent knee-jerks. Implication of lateral columns in such flaccid cases is shown by the Babinski response. This type of case has a rapid course. Rarely the

disease is confined to the posterior columns, and when this is so, there are no signs of involvement of the pyramidal tract. In this state of partial paraplegia the patient may remain for years. The paraplegia usually progresses, but not uniformly. Sudden exacerbations of symptoms may occur at any time, with associated malaise, pyrexia, vomiting, and diarrhoea, and perhaps by an increase in the anaemia. As the disease advances it involves more and more of the trunk. In some cases the upper limbs are affected early and may even be the first to show signs of disease. In the course of time the paraplegia becomes complete, as does the wasting of muscles and reduction of faradic excitability. However, when this occurs it is usual for spasticity to disappear; with the onset of flaccid paraplegia with lost or diminished knee jerks, the superficial reflexes and Babinski remaining. Sometimes the spastic state persists to the end in spite of absolute paraplegia and total sensory loss. In these cases flexor spasm may develop.

As a rule the condition of the upper extremities remains one of partial paralysis only, most marked in the periphery, with wasting of muscles of hands and forearms. There is also conspicuous wasting of subcutaneous fat. Sphincter control becomes impaired and lost usually in the late stages, but sometimes is lost fairly early. Incontinence or urine and faeces is usually late, but partial incontinence or retention of urine is not uncommon in the earlier stages. Loss of sexual power in the male is often an early symptom. The persistence of a high degree of reflex excitability of the skin of the limbs and trunk is a common feature. Plantar reflexes assume the extensor type early and usually remain so throughout the course of the disease. In the lower extremity all degrees of change and variation may be found in reflexes, but here as elsewhere the lower parts are more severely and constantly involved. The presence or absence of tendon reflexes is, however, no index of the severity of the cord lesions. Hence, in many cases with weak flaccid legs and severe impairment of joint and vibration sense, the tendon jerks may be present, whereas in others with only moderate weakness, the joint sense is good, vibration sense is reduced, but knee and ankle jerks may be absent. Ankle jerks are frequently found absent and patellar present, but variations in tendon reflexes during the course of the disease may be found. The most likely place for the reflex arc to be interrupted would be at the dorsal root entry zone — a situation where degenerative changes can occasionally be demonstrated pathologically.

Mental symptoms are not an uncommon accompaniment of sub-acute combined degeneration and pernicious anaemia. These take the form of slow cerebration and impaired memory, perception, and attention, in a large number of cases. Confusion, disorientation, change of personality, depression, irritability, delusions of grandeur and persecution and also euphoria and somnolence are sometimes seen. Paranoid tendencies are not common. It is only rarely that definite psychotic states develop. There appears to be no law according to which these mental disturbances develop and psychic changes may run the whole gamut of mental symptomatology. It is thought that an individual predisposition is present in many cases, but when this is not so, the psychosis may then be placed in the category of exhaustion or infection intoxication psychosis. Just as cord symptoms may appear long before development of pernicious anaemia so may mental symptoms, which may be transitory and changeable, become manifest. There is a most striking lack of corelation between pathological lesions found in the brain and clinical symptoms. The development of well marked psychotic manifestations is probably independent of pernicious anaemia.

Involvement of cranial nerves is usually accidental, with the exception of loss of disturbance of hearing and smell. This is part of the neurological picture of subacute combined degeneration, since it accompanies and is associated with the development of other symptoms. Cranial nerve changes when present are of little or no early diagnostic significance. There is no predominantly characteristic involvement to be demonstrated. A mild degree of nystagmus is a fairly common finding and may depend on involvement of the cervical sympathetic. The pupils may be small, irregular, unequal and react poorly to light. There may be narrowing of the palpebral orifice and exophthalmos from involvement of the cervical sympathetic. Herpes is not infrequent. Trophic changes occur frequently in later stages, chiefly in nails and skin, while vasomotor disturbances in the periphery and bed sores are common. Soft translucent oedema of the extremities and trunk is frequent when the anaemia is severe, and is dependent on the anaemia as well as the impaired innervation. Severe and painful but transient local oedema has occurred in some cases. As previously stated, signs of pernicious anaemia are absent in about 1/3 of the cases. In these cases achlorhydria is a constant finding, while the haemoglobin and blood picture may be normal, and remain so until late in the course of the disease. Most cases show a haemoglobin of over 55%. Others may show a slight anaemia with the typical blood picture of pernicious anaemia. The majority of cases, however, show the blood picture of pernicious anaemia regardless of the Hb. There is no correlation between the blood picture and haemoglobin and neurological symptoms. Remissions in blood picture are accompanied by remissions in neurological and mental symptoms, but there may be a progressive rise in haemoglobin and improvement in blood picture, with neurological signs and symptoms becoming steadily worse, especially with inadequate liver therapy. There is also lack of correlation between neurological and mental symptoms and signs and the pathological condition found at autopsy. The clinical picture may be one of advanced cord involvement with the patient bed-ridden, whereas the cord may show little change. The reverse is also true, especially in long-standing cases. Fever is present in about two-thirds of the cases, at some time during the course of the disease. It is most common in acute cases, but bears no relation to the severity or condition of the blood picture. It may be irregular, intermittent or continuous. Any intercurrent infection causes sudden progression of the neurological symptoms.

In concluding, the writer wishes to express his indebtedness to Dr. Linell and especially to Dr. Hyland, for the free use of his unpublished material, in preparing this paper.

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THE PIONEER HEALTH CENTER

A NOVEL SOCIAL EXPERIMENT

By AGNES I. RUSSELL, '38.

Nine years ago, in a small house in Peckham, London, two medically-trained biologists began an experiment. They were seeking not for disease, but for health—and, to them, health was not the mere absence of disease. They realised that there are two menaces to health: disease, and devitalisation. They planned to apply the methods of a scientific laboratory to the study of a group of men, women, and children living under the normal conditions of present-day life. But the experiment was to be more than just a means of amassing a great deal of scientific data: it was to be a combination of biological research with a unique social experiment. Thus the Pioneer Health Centre was formed.

Under ordinary circumstances, it is the patient who makes the diagnosis, and often the doctor does not see him until he is really ill. Now, although medical science has advanced far, the fact remains that anything mended is rarely as good as something which has not been broken. In the Peckham experiment, the usual procedure was changed. Families in the district were invited to join the Centre, paying sixpence a week, and for this, the father and mother were given an annual medical examination; the adolescents, a bi-yearly overhaul; the children of school age, an examination every three months; and the infants, a weekly examination. In this way, the doctor might decide whether the members were ill or well. No medical or dental treatment was given, but the patients were sent to a hospital or to their own doctors.

Soon it was seen that prescriptions a little out of the ordinary must be given. For a woman tired out by hard work and the care of small children, an afternoon at the Centre would be prescribed; and, while she was being taught bridge, or dressmaking, or was having a quiet afternoon chat, her children would be learning games and songs in the nursery. A flat-chested, unathletic boy might receive the following prescription:

R/ Swimming: 20 minutes 3 times weekly.
Draft into team X: 3 months.

He would be pitted against those who were more or less his equals, so that he might not lose his self-respect. Members of the Club were allowed to use the building during the afternoon and evening, and the Health Centre became a social centre, where men and women and children could meet, and mix, and enjoy life together, and thus could become richer socially and mentally.

At the end of three years, the Centre was closed. A great deal of scientific data had been collected, and it had to be examined and interpreted before it could be utilised. Then, too, the experiment had succeeded so well that much better accommodation was necessary in order to carry on the work.

The survey revealed the surprising fact that there was something to be done for all the parents over twenty-five years of age, and that ninety percent of them were definitely diseased. There were those with diseases which they themselves recognized but they had not consulted a doctor for various reasons. The disease was bearable, and they were able to carry on their work. Many of the women felt that they could not be

spared from their homes and that they would have to go on until they dropped. Some of the men could not afford to miss days of work, and others, who were not really ill, were afraid to consult the doctors at the hospitals, so busy with urgent cases. Such an institution as the Pioneer Health Centre, situated right in the district where the people live, is able to bring an individual to treatment early, and also to provide for after-care.

Besides those adults who were frankly diseased, there were those with hidden diseases. Even if opportunity for early treatment were provided, these individuals would not make use of it, for they are unaware of disease. Healthy organs in the body are compensating for the unhealthy organ, and this is done so well that the disease may remain masked for a long time. The diagnosis of ill-health should not depend upon the patient, because often, only in the case of an emergency when extra energy is needed, does he find out that something is wrong.

A third group of adults were found to be half way between health and disease because of certain physical and mental conditions which are the precursors of disease. Many had bad habits which were liable to produce disease, and these individuals needed advice. By correction of these habits, the Pioneer Health Centre was able to prevent the onset of disease. Others were suffering from maladjustments, physical or psychological. Physical maladjustments such as glasses which needed changing, shoes which are too tight, trusses which need adjusting, trivial in themselves, often have a great influence on the individual, and may cause bad temper, moroseness and fatigue. Psychological maladjustments can be much more serious, and are reflected on the home and the children. Often, the Pioneer Health Centre, through its Family Club, brought about the needed adjustment. A few years ago, the doctor always lived among his people, and shared their social life, and he was in a position to observe individuals in their own environment, and to prevent disease. Now, in large towns and cities, the doctor does not live where he can get any real knowledge of the lives of the families he serves. The Centre has formed a relationship similar to that which existed formerly between the patient and his family doctor.

Among the adolescents, actual disease was rare, but most of them were found to be devitalised, physically and mentally. The conditions met with were nutritional deficiencies, statural defects, and functional maladjustment. Some of these conditions could be removed, and others helped. Many with no physical defects showed that they had grown up in a very poor environment, and their energies were being diverted into undesirable channels. There were others who were well physically and mentally, and who needed an opportunity for the development which was lacking.

The school child was found to have two main classes of disorder. The one was nutritional disorder, which could be observed often in the whole family. The school doctor sees only the individual child, but at the Centre, the doctor saw all the members of the family, and this helped him in his examination. The other class of disorder was structural and functional disability, such as flat feet, flat chests, and slowness of speech. Special prescriptions had to be given in order to correct these.

The children's nursery was used as a means of early detection of disease in the small children. Much more can be learned by watching a child in action than by examining him in a consulting-room, strange and unfamiliar to him. The nursery was also a place for remedying defects. The child who was slow in speech, the child who was clumsy, the child who was spoiled and

unmanageable, the child who was repressed too much at home—each received the necessary treatment, and improved rapidly.

Preventive medicine has been in practice in infant welfare work for many years. However there are some limitations to these clinics: the practitioner does not live among his people, and often, in an emergency, he cannot be reached; there is no obligation to attend constantly, and the mother's attendance is often very irregular; treatment of the mother is beyond the scope of the clinic. These difficulties were removed in the organization of the Pioneer Health Centre.

The summarised conclusions of the experiment were these: that the individual and his environment cannot be separated; that to develop the health of a child, one must promote family welfare; that the artisan populace is willing and eager to submit to periodic medical examination; that disease which is so prevalent in the adult population remains untreated for the most part; that such an organization as the Pioneer Health Centre removes the burden of disease detection from patient to doctor; that in youth, there is a latent power which may be used in the cause of health, or may become a source of disease; that this latent potentiality should be developed; that the artisan is willing to pay for the maintenance of his own and his family's health, and does not need charity; that the only really effective method of attacking disease is to preserve health in the home, and in every member of it.

A research worker often performs his first experiment in the laboratory, and then he continues, on a larger scale, with his "field" experiment. The small "laboratory" experiment has been very successful, and last month the "field" experiment was begun when the new Pioneer Health Centre opened. It is to be run on the same lines as before, but will include the elements lacking in the first experiment. It will be a focus of endeavour toward health — truly a Health Centre.

A site of about two acres was bought, and on it a fine building has been erected. It is the work of Sir Owen Williams, and its architecture is as remarkable as its function. It will accommodate two thousand families, and, with a subscription of one shilling a week per family, as well as smaller fees for membership in intramural clubs, the Centre will be self-supporting.

In the building, there is a large, main hall, with a self-service cafeteria in the centre, and a dance floor at each end. It is to be something like a continental café, and will be a meeting-place for the whole family. The swimming pool is large, completely enclosed in glass, so that spectators need not sit in the warm, damp atmosphere of the pool. The corridors around it are to be used for fencing, billiards, bowling, and quieter games, and, in the afternoons, for tea-rooms and work-rooms. There is an afternoon nursery for the children, and an infants' nursery for the babies. Reading cubicles will provide a quiet place for children to study, and there will be reference books. A library in the ordinary sense is not necessary, for there are plenty of public libraries; but a librarian will be there to give the children the stimulus to read. The gymnasium will serve as an auditorium, and there is also a smaller hall for lectures, debates, and music. The rest of the building is taken up with medical consultation rooms and administration offices, and there is a large space to be used as research laboritories when there are sufficient funds to offer reasonable salaries to suitable workers.

The members taking part in the various activities will be organised into intramural clubs. They will be drafted into these by prescription, after the medical examination, and everything will be done to make mem-

bership a pleasure. The Centre will be made a focus of infection, for the sight of others engaged in some absorbing activity is infectious, and a number of enthusiastic Doers will be invited there from time to time. These activities are all being provided in order to promote the physical and mental happiness and health of the members, for the purpose of the Centre is essentially the prevention of disease and the cultivation of health in the family.

In the future, the doctor's task, like that of his Chinese confrère, will be to keep his patients well, and preventable disease will be regarded as a reflection on him. This will be possible only when, through some suitable organisation, doctor and individual are brought face to face while disease is still in its initial stages.

A MODERN CONCEPTION OF THE PHYSIOLOGY OF THE AUTONOMIC NERVOUS SYSTEM

By J. P. FLETCHER, M.A., '37.

The function of the nervous system is to the author the most fascinating aspect of physiology and pathological physiology. In the past great strides in the elucidation of the physiology of the voluntary nervous system have been made, by Sherrington and Adrian in particular, but until rather recently only the general functions of the autonomic system were clearly understood. This is rather susprising for, since it concerns the basic life processes, its clinical importance can hardly be overemphasized.

Since an accurate understanding of the neural pathways of the autonomic system is essential, they will be reviewed from a historical aspect. The sympathetic chain of ganglia were once considered to be an independent nervous system controlling the viscera and connecting with the central nervous system. But, Gaskell showed histologically that the non-medullated fibres from these ganglia entered the corresponding spinal nerve subsequently to pass peripherally except for a few fibres running centrally to supply the blood vessels of the meninges of the spinal cord. Embryological studies by Onodi showed that the sympathetic ganglia and posterior root ganglia migrate from the postero-lateral part of the spinal cord so that the former are motor cell bodies of the central nervous system, as Langley showed. Thus the sympathetic system is preferably called the "Thoraco-lumbar outflow" of the central nervous system and it consists of a short connector axone from the spinal cord to the ganglia and a long motor axome to the gland or smooth muscle cells.

The less obvious part of the autonomic nervous system, commonly called the parasympathetic, was discovered partly histologically. The lateral roots of the upper cervical cord form the spinal accessory nerve which runs in the vagus. The lateral horns of the sacral cord segments 2 and 3 form the pelvic nerve which connects with short motor neurones lying on the bladder and rectum, which they supply. Similarly it was shown that cranial nerves III, VII, IX, and X are connector axones to motor neurones lying close to the structures which they innervate.

The cranial and sacral outflows of the central nervous system produce similar effects in the separate regions which they supply, whereas the thoraco-lumbar outflow tends to reverse these effects. Therefore, we may separate the antonomic system into Bulbo-

sacral and Thoraco-lumbar portions. Electrical stimulation of autonomic nerves suggests that in general, the functions may be condensed into the statements that the Thoraco-lumbar is concerned with dissipation of energy whereas the Bulbo-sacral stores and conserves energy. Each of these stimulates certain smooth muscle and gland cells and at the same time inhibits others incompatible with the activity of the former.

Unfortunately the simple concept that the Thoraco-lumbar reverses the action of the Bulbo-sacral and vice versa does not apply without modification to many important autonomic actions, some of which will be mentioned:—

(i) General thoraco-lumbar action results in dilatation of coronary arterioles with constriction of those of splanchnic area and skin.

(ii) Thoraco-lumbar sends vasoconstrictor and possibly vasodilator fibres to kidney arterioles while the Bulbo-sacral do not appear to send any.

(iii) The effect of Thoraco-lumbar and Bulbo-sacral on stomach muscle varies greatly with pre-existing tone.

(iv) The sweat glands are innervated by Thoraco-lumbar yet adrenaline (which simulates its action) does not cause secretion (except in a few animals, notably the horse) while pilocarpine (a bulbo-sacral stimulating drug) causes secretion and atropine (Bulbo-sacral paralyzing drug) prevents secretion.

(v) The spleen has Thoraco-lumbar innervation only, yet both pilocarpine and adrenaline cause it to contract

(vi) In uterus, Thoraco-lumbar and adrenaline cause either increase or inhibition of both tonus and movements, yet pilocarpine stimulates and atropine depresses both tone and movements.

(vii) Species differences in response of some particular organ to each part of the autonomic system are very marked.

Such confusion assures us that only a part of the mechanism of autonomic nervous action had been appreciated at this stage.

The first intimation that chemistry might prove of major importance in the mechanism of nervous action was given by Oliver and Schafer who found that injection of an aqueous extract of adrenal medulla caused a great rise in blood pressure, due to arteriolar constriction. Takamine isolated the active substance which proved to be a simple tyrosine derivative and can be synthesized.

Thus it was shown that the Thoraco-lumbar could act at a distance and for a prolonged period through the release into the blood stream of a relatively simple chemical substance.

The more difficult but analagous discovery that the vagus nerve liberates a substance which appears in heart perfusion fluid so that the latter produces vagus effects upon a normal heart was made by Loewi and coworkers (1921-1926). Subsequent work by Loewi and many others shows that this substance cannot be distinguished from acetyl choline and is apparently released by active Bulbo-sacral effector autonomic nerves all over the body and is biologically active in very many species, even including the invertebrates. In contradistinction to adrenaline, this hormone acts locally only, because it is very rapidly rendered inert by an enzyme in blood and tissues. Recent work by Henderson and Roepke suggests that there is likely another chemical substance released at the site of Bulbo-sacral action which is concerned with smooth muscle movements while acetyl choline appears to control tonus exclusively.

Concurrently, parallel work on the mechanism of action of Thoraco-lumbar effector endings by Cannon and Rosenblueth has brought forth very interesting results which have not (to

the author's knowledge) been contradicted. Stimulation of hypogastric or hepatic nerves (Thoraco-lumbar) in the cat results in liberation of a substance which enters the blood stream and causes acceleration of heart rate, rise in blood pressure, flow of saliva, contraction of nictitating membrane, spleen and pregnant uterus. All these effects are also produced by adrenaline but evidence that this substance is distinct from adrenaline is given by comparison of the effects of each after ergotoxin injection, which paralyzes the motor functions of adrenaline. Thus, after ergotoxin, adrenaline causes only a fall in blood pressure due to pure vasodilatation, whereas hepatic stimulation results in a simple rise in blood pressure and abdominal Thoraco-lumbar stimulation produces slight blood pressure fall followed by a prolonged rise. These diverse effects result from doses of adrenaline and hepatic stimulation which produce equal acceleration of heart rate without ergotoxin. Other experimental evidence is offered in support of the existence of a Thoraco-lumbar chemical mediator which Cannon calls "Sympathin." The fundamental difference between adrenaline and sympathin action appears to be that adrenaline can cause both contraction and relaxation of smooth muscles of blood vessels, whereas sympathin causes contraction only, even after ergotoxin. Further study by Cannon and Rosenblueth suggests that there may be two kinds of sympathin, one concerned with contraction, the other with relaxation of smooth muscles other than those of arterioles. Their evidence is the finding that stimulation of the hepatic nerve results in contraction of the nictitating membrane of the eye of the cat but having no effect on the denervated virgin uterus, whereas splanchnic nerve stimulation and adrenaline result in contraction of the nicitating membrane and relaxation of the denervated virgin uterus. Of course, this work will have to be verified before it can be accepted.

Future research along the lines indicated by the discovery of chemical mediators for both Bulbo-sacral and Thoraco-lumbar (if the latter proves to be an entity) may result in great practical applications. Cannon suggests that synthesis of Sympathin E (excitatory to smooth muscle of certain tissues, for example, nictitating membrane, arterioles) and of Sympathin I (inhibitory to smooth muscle of certain tissues, for example, virgin denervated uterus, arterioles) would allow more discrimination in therapeutics. For example, by injection of Sympathin E the heart could be accelerated and the blood pressure raised without inhibiting the digestive processes.

The mechanism of automonic action by means of release of chemical mediators (acetyl choline and sympathin) at the effector smooth muscle or gland may offer the correct explanation of some of the discrepancies to the simple theory, which were noted above. For example, the dilatation of coronary arterioles in response to adrenaline injection may be due to the faculty of the coronary artery smooth muscle fibres to convert adrenaline into Sympathin I, producing vaco-dilatation, whereas, the splanchnic and skin arterioles may convert adrenaline into Sympathin E, producing vasoconstriction. Thus the redistribution of circulating blood by adrenaline is effected.

Very important experiments within the last two years suggest that a drastic change in our conception of the distinctness of the Thoraco-lumbar from the Bulbo-sacral autonomic may have to be made. Feldberg and co-workers show that stimulation of the splanchnic nerve results in accumulation of a substance in the adrenal medulla indistinguishable from acetyl choline and in adrenaline release into the blood stream. More important still is their experiment on

the perfused superior cervical ganglion in which stimulation of the preganglionic (connector) fibres results in the release of the substance indistinguishable from acetyl choline in the venous blood from the gland. Addition of small amounts of acetyl choline to the gland perfusion fluid results in contraction of the nicitating membrane. Also, the presence of eserine (which potentiates the action of acetyl choline) lowers the threshold to both small doses of acetyl choline and submaximal preganglionic nerve stimulation. All the above work appears to have been controlled with great care. The authors interpret their results in the following manner:— A substance indistinguishable from acetyl choline is released at the Thoraco-autonomic endings in the adrenal medulla and effects the release of adrenaline. In the superior cervical ganglion, the substance biologically indistinguishable from acetyl choline is released by the nervous impulse passing down the preganglionic fibres to the synapse. Therefore, this chemical substance may act as mediator or transmitter of Thoraco-lumbar activity.

These results have led Sir Henry Dale, in whose laboratory almost all of them were obtained, to suggest that autonomic nerve fibres should be classified according to the chemical mediator released by them rather than according to their anatomical pathways. He proposes the terms "cholinergic" and "adrenergic" autonomic nerves. If we accept this theory, an explanation is presented for the apparent anomaly that the sweat glands are innervated by the so-called Thoraco-lumbar nerves but are affected only by Bulbo-sacral inhibiting and simulating drugs. Thus—"Thoraco-lumbar" fibres to sweat glands are cholinergic, releasing "acetyl choline" at the gland cells. That such is the case is proven by experiments in Dale's laboratory in which a substance biologically indistinguishable from acetyl choline was detected in the venous blood from the sweating hairless pads of the cat's foot following lumbar-autonomic stimulation.

That is fibres of the Bulbo-sacral outflow release a substance indistinguishable from acetyl choline at both synapses and effector endings (choinergic fibres) whereas fibres of the Thoraco-lumbar outflow release the same substance at synapses and at some effector endings (cholinergic fibres) but release Sympathin E or Sympathin I at the other effector endings (adrenergic fibres).

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TRAUMATIC LESIONS OF THE SUPRASPINATUS TENDON

By B. J. WOODS, B.Sc., '35.

Anatomy. The shoulder joint is an enarthrodial or ball and socket type of joint. It is very prone to injury because its bony socket is shallow and vertical; what it gains in mobility it loses in stability; it forms an exposed prominence on the body surface; and the capsule and ligaments are necessarily lax in order to allow for the requisite range of motion. This leaves one great source of strength for the joint, the surrounding muscles and tendons, and these have a more intimate relation to this joint than is found in any other joint in the body. The muscles of the shoulder girdle all converge in the form of a cone from the chest wall to the upper end of the humerus, and the axis of this cone points outwards and slightly upwards. But the muscles most concerned in the support of the joint are: (1) above, the supraspinatus; (2) behind, the infraspinatus and teres minor; (3) below, the long head of the triceps; (4) anteriorly, the subscapularis. We should think of the group of short rotators (1), (2), and (4) not as separate tendons about the joint, but as forming a single musculo-tendinous cuff, which is incorporated in the capsule of the joint, and which gains insertion partly into the facets of the tuberosities and partly into the anatomical neck of the humerus.

Of the ligaments of the shoulder only one is of great importance, the coraco-acromial. Its function is to restrain undue upward movement of the head of the humerus and hence together with its two bony attachments, it forms a secondary shoulder joint.

The largest and most important bursa about this joint is the Subacromial; in the cadaver it is about 1½ inches in diameter, concavo-convex in shape and arbitrarily divided into three parts: (1) the subacromial portion, lying between the acromion and the tendinous expansion of the supraspinatus; (2) the subdeltoid portion, between the under surface of the detoid and the tendinous expansion of the short rotators, and (3) the subcoracoid portion, between the coracoid process and the coraco-acromial ligament and the capsule of the joint. These various parts of this bursa may be separated by incomplete membraneous partitions. It will be appreciated that this bursa really amounts to a synovial membrane for the above-mentioned secondary shoulder joint, and it never communicates with the true shoulder joint.

Physiology. The great function of the shoulder joint is mobility, but as the scapula takes a part in practically all movements the range of the scapulo-humeral joint is difficult to determine and necessarily only approximate.

Elevation of the shoulder in the coronal plane, as Lockhart points out is a continuous combination of movements of the scapula, sterno-clavicular and scapulo-humeral joints. This Codman has named normal scapulo-humeral rhythm. It cannot be divided into two separate components such as movement at the scapulo-humeral joint till the arm reaches the horizontal, and thereafter rotation of the scapula to raise the arm to the vertical position. In this movement the contraction of the deltoid, from the direction of its fibers would tend to press the head of the humerus up un-

der the acromion, which is not a suitable fulcrum to lever the humerus on, because it has no articular cartilage. But the supraspinatus by virtue of its more horizontal course utilizes the glenoid as a suitable fulcrum upon which the power of the deltoid can act.

Incidence. The incidence of rupture of the supraspinatus tendon with or without involvement of the subacromial bursa is surprisingly high judging from autopsy reports. Akerson and Codman made the first survey in this field in 1931 when they reported 39% in 100 consecutive shoulders coming to autopsy. In a later series the same workers found the lesion in 25%. In half of these cases the rent was gross enough that the articular surface of the head of the humerus could be seen on opening the subacromial bursa. Our own Department of Anatomy (U. of T.) under Dr. J. C. B. Grant has found 10 such lesions in 25 cadavers or 40% of all which were complete enough to give free communication between joint and bursa, and all of which were bilateral.

Aeticlogy. The underlying cause of this pathology of tendon and bursa seems not to be infection for these reasons: (1) it has no constant relationship to any other foci of infection within the body; (2) cultures taken from such joints have always been found sterile; (3) operative incisions into these joints invariably heal by first intention. That degenerative changes play some part is indicated by the fact that (1) most cases are in the older patients, and (2) autopsy findings indicate that the lesion is very often bilateral. But trauma plays at least a definite precipitating role in the etiology because (1) in all of Codman's cases which he confirmed by operation, (something over 40) there was a definite history of trauma, with the exception of 2 cases (which were known to have been drunkards and may well have received the trauma unknowingly) and (2) many cases do well after operative repair, and this is not what one would expect if the lesion were to any extent degenerative.

Pathology. The pathology found in operative and autopsy studies consists of lesions of the bursa, the musculo-tendinous cuff, the bones, and the shoulder joint proper. (1) *Lesions of the subacromial bursa.* The lesion most frequently found consists of synovial villi representing the remnants of adhesions while adhesions and bands between the base and the roof of the bursa are common. In some of the more chronic cases, calcified particles are found in the bursa; these Codman believes to have originated in the tendon and ruptured into the bursa. (2) *Lesions of the musculo-tendinous cuff.* Calcified deposits are common, but being temporary and giving no symptoms often, they are missed clinically even in the presence of an X-ray because they are so often superimposed on the more radio-opaque bones. It is not at all certain whether these deposits may be caused by trauma or whether they always anti-date the trauma. Rupture of a portion of the musculo-tendinous cuff is by no means rare, and is most often of that portion which represents the supraspinatus tendon. Retraction of the torn muscle fibers makes the rent triangular in shape. The margins of the tear become rounded off and falciform in shape but healing is slow both because of the poor blood supply to the tendon and the gaping nature of the rent. When the tendon is avulsed from the bone, there is still less chance of healing without interference but since the base of the bursa is attached to both tendon and tuberosity, injury to the bursa is less likely; and this may explain why these cases recover more promptly than rupture of the tendon. Partial ruptures of the tendon are seen as well as complete. (3) *Lesions of the bony parts.* In cases where the complete rupture of the supraspinatus tendon has been present for any considerable length of time, the greater tuberosity shows hypertrophic changes in the

nature of irregular bony excrescences, which are said to be the result of an irritative osteitis from the impinging of the greater tuberosity on the acromion in elevation of the arm. Ebrunation of a portion of the greater tuberosity and of the under surface of the acromion are often seen in old standing cases, again the result of continual friction. (4) *Lesions of the shoulder joint proper.* The articular cartilage of the head of the humerus is commonly found eroded, where it has been exposed by a rent, near the superior facet of the greater tuberosity. In more recent cases an excess of joint fluid is found at operation. This may be palpable as a fluctuant swelling in the apex of the axilla, or demonstrated by elevating the arm which tenses the lower part of the capsule and forces the fluid up into the subacromial bursa, if this is in communication through a rent.

Clinical. Following trauma, painful shoulders, in the absence of such apparent lesions as fracture, dislocations and tumors, etc., are most often due to one of four clinical entities: (1) complete rupture of the supraspinatus tendon, (2) incomplete rupture of the supraspinatus tendon, (3) calcified deposits in this tendon, or (4) tendinitis and bursitis.

(1) *Complete rupture of the supraspinatus tendon.* The following points in history and examination are of most importance in diagnosing this condition. The condition usually occurs in persons over 50 years of age, with about 90% of cases in males. It is much more common in the labouring classes, because of overuse, and greater exposure to trauma and accident. In the history of the injury the importance seems to lie in the suddenness with which the patient throws out his arm rather than in any direct violence to the shoulder, so that tearing of the tendon results from a sudden contraction of the muscle against the inertia of the arm. This may be followed by a momentary sharp jab of pain in the shoulder or a sensation of something having given way. This is typically followed by a lucid interval of a few hours after which a more or less continuous pain is felt about the joint. This interval is said to be due to the avascularity of the tendon, so that it takes some time for enough hemorrhage to occur to distend the joint or bursa.

Examination will show inability or great weakness on elevation of the arm in the coronal plane when the scapula is fixed and the patient erect, but much greater movement in the same plane occurs when the patient stoops over. This is due to the fact that in the stooped posture the humerus is swung as a pendulum by the deltoid; whereas in the erect posture, it is raised as a lever requiring the contraction of the supraspinatus to hold it to its proper fulcrum. Faulty scapulo-humeral rhythm will be present so that on elevation without the scapula being fixed, ascent to the horizontal will be wholly scapular movement. In the same way if the arm is put into the position of complete elevation, the first half of the descent of the arm will again be scapular movement because muscle spasm inhibits movement at the painful joint till compensatory movements can no longer take its place.

Tenderness will be present just proximal to the superior part of the greater tuberosity over the ruptured tendon, but in some cases the patient is most tender at the insertion of the deltoid. A sulcus may be palpable between the two fragments of the torn tendon which in some cases corresponds to the anatomical neck of the humerus. On elevation, this sulcus slipping under the acromion causes a visible and palpable jog in the movement, and at the same time causes the patient to wince slightly. There is a sense of relief and an absence of any tender joint when the arm is fully elevated, because in that position the rupture of the tendon

has glided beneath the protection of the acromion.

An excess of joint fluid is often found and in complete ruptures this can be made to pass into the subacromial bursa by the manoeuver described above. Atrophy of the supraspinatus muscle may be noticeable in three weeks, the spine of the scapula appearing more prominent on the affected side. The infraspinatus muscle often shows atrophy as well, possibly because the tear has been extensive enough to involve its tendon as well. The deltoid is seldom atrophied except from general disuse of the limb. X-rays are negative except in cases of evulsion of a portion of the greater tuberosity.

(2) *Incomplete rupture of the supraspinatus tendon.* The age, sex, occupational incidence and history of inquiry are about the same as for complete ruptures, but on examination, the range and power of elevation are not interfered with to anything like the same extent, and all the other signs mentioned are less pronounced, especially the atrophy. In incomplete rupture where the bursa and joint do not communicate, either may be distended with fluid independently of the other; this sign can never occur in complete rupture of the tendon.

(3) *Calcified Deposits in the Supraspinatus Tendon.* The commonly used term for this lesion is calcified subdeltoid bursitis, but the calcification occurs primarily in the tendinous base of the bursa, and bursitis results only from the rupture of these calcareous particles into the bursa. The age of greatest incidence is a few years younger than ruptures, with about one-third of the cases occurring in females. The occupation is usually one less strenuous than that of a labourer, commonly occurring in professional men and stenographers. There is a very much less definite relation to history of trauma, and indeed Codman believes it is related to excessive use rather than to trauma which simply exaggerates the symptoms. There is no history of acute onset of painful shoulder in these cases but rather a gradual onset of a painful hitch on elevation of the arm, accompanied by a loss of normal scapulo-humeral rhythm and general disuse atrophy of the muscles of the shoulder girdle. More acute pain and spasm may be precipitated by trauma causing the deposit to be infiltrated by leucocytes forming sterile pus which tends to point into the base of the bursa, so producing pain due to tension, and to friction of the bursa. X-rays are of especial value in the diagnosis of this condition but if the clinical findings are typical, it will be necessary to X-ray the shoulder from 4 to 5 directions before pronouncing it negative, as the deposit may be easily missed by being superimposed on neighbouring bony structures.

(4) *Tendinitis and Bursitis.* This condition is usually known as Adhesive Subacromial Bursitis or Frozen Shoulder. Codman believes that the bursitis is always due to a tendinitis usually caused by some slight trauma or overuse and it is conceivable that even ruptures of a few fibers of the supraspinatus might give rise to a very stiff and painful shoulder, consequent upon the formation of adhesions with matting together of the roof and base of the subacromial bursa. The age is about the same as for calcified deposits. The sex distribution is equal while the incidence is highest in men and women of leisure. There is usually a history of slight trauma or overuse. The differentiation of tendinitis and calcified deposit is very difficult or impossible on clinical grounds, without the use of X-rays. Adhesive subacromial bursitis gives marked limitation of both active and passive movements, so that in complete adhesion of this bursa, one-half of the scapulo-humeral elevation and 140 degrees of rotation are said to be lost. As a rule the greater the limitation of movement the less painful is the shoulder.

Treatment. *Rupture of the tendon.*

For reasons given above it seems clear that there is practically no chance of a union of the separated stubs of tendon if a non-operative course is followed. This is true of all cases of complete ruptures and in those cases of incomplete rupture where there is communication between the joint and the bursa. Therefore, in this group of cases, operation is advised as soon as the diagnosis can be made.

Codman and Wilson have described two good methods of approach to the shoulder joint. In each the object is the same, namely, to repair the ruptured tendon and to make the bursal surfaces as frictionless as possible. The retracted supraspinatus tension is sought under the acromion pulled down and sutured by means of silk or fascia lata to the shorter stub. This reconstructs the floor of the bursa. Codman does not suture the roof of the bursa because he believes this best left open to allow blood and exudate to seep out and thus minimize adhesions. In cases where re-suture of the tendon is impossible, excision of the greater tuberosity may be a good means of cutting down friction and eliminating the painful jog on elevation of the arm.

The post-operative treatment is very important. A pad is placed in the axilla and the arm is allowed to rest on a pillow in a partly elevated position. After a matter of a few days, exercises are begun in the stooped position, to minimize the formation of adhesions. Later, exercises are taken in the erect position. The patient usually requires hospitalization for about 2 weeks but a period of a few months is necessary before a complete range of painless movement can be expected. Codman reports, in a series of 31 cases. good results in 20, fair in 7, poor in 4, with none made worse by the operation.

In those cases of incomplete rupture where the joint and bursa do not communicate, there is no retraction, and healing usually takes place in the course of a few months, so there is no indication for operation. A logical treatment would consist in the fixation of the arm in the position of 90° elevation, in order to relax the torn tendon, the splint used in fixation being removable so that at intervals the patient might take stooping exercises to prevent the formation of adhesions. In cases where there is doubt as to the extent of the tear, a small exploratory incision is indicated.

Calcified Deposits. All of these cases make a good recovery with or without treatment and it is only a matter of time and discomfort. So that in all very painful cases and in cases where the deposit is as large as a lima bean, Codman advises surgical removal. The same post-operative treatment is used as for ruptures, but the patient may expect full use of his arm in six weeks.

Tendinitis. Cases of tendinitis of the supraspinatus always recover in 1-2 years and because the disability is not great and the incidence is highest in people of leisure, treatment is rarely necessary. When there is more than usual pain, rest in bed for 1-2 weeks with the arm partly elevated and resting on a pillow is usually all that is required. If adhesions of the bursa result from the tendinitis, a full range of manipulation under an anesthetic is indicated. This must be done with some care, as vigorous rotary movements in the presence of firm adhesions have been known to result in spiral fracture of the shaft of the humerus. In rare cases adhesions may be so complete that manipulation is of no avail, and for this Goldthwait and others have recommended operation and excision of the bursa. Following manipulation or excision, for adhesions the treatment consists of (1) rest in the semi-elevated position and (2) a course of gradually increasing movements in all directions, to prevent the reformation of adhesions.

BLOOD CLOTTING --- THEORETICAL ASPECT

By R. ALEXANDER MUSTARD, B.A.

Introduction: In all animals there occurs, in the blood which leaves the vessels and flows out over the wound. a characteristic phenomenon which is called, briefly, "clotting." Gross examination reveals the process to consist in the development of a gel from the previously liquid blood. The gel exhibits syneresis, and in shrinking exudes a pale, straw-coloured, "serum." Microscopic examination of the clotting process reveals the deposition of needle-shaped crystals in the previously clear fluid. These needles vary in length from 10-30 microns. As clotting progresses they mass to form a dense meshwork. The clot may be washed free from serum and entangled cells and examined. It is found to consist of a very insoluble protein which is called *fibrin*. Its precursor in plasma is called "*fibrinogen.*"

In an investigation of the mechanism of blood coagulation we must take cognizance of certain facts which have revealed themselves to almost every worker in the field. (1) Spontaneous clotting can not occur in the absence of calcium ions. Precipitation of blood calcium by the addition of a soluble oxalate, or depression of the ionization of calcium by the addition of citrate or fluoride preserves the fluidity of the blood so treated. (2) Tissue juices accelerate clotting. Blood flowing out over a wound clots more quickly than blood drawn by a cannula into a clean vessel. Tissue juices however will not initiate or accelerate clotting in the absence of calcium ions. (3) There is present in fresh serum a factor which will cause rapid coagulation even of decalcified blood. It was early recognized that the generation of this factor in blood was probably ultimately responsible for the clotting phenomenon. "*Thombin*" was the name assigned to this agent. Since obviously it could not exist in normal intravascular blood, it must have some precursor, and to this hypothetical precursor the name "*prothrombin*" was given.

The acceptance of these facts involves the assumption of at least five elements in the clotting system: (1) fibrinogen, the precursor of fibrin, (2) the active principle in tissue juices. (Without making any assumption as to its action we shall call it, briefly "*kinase.*" This agent may be supplied by blood cells as well as by the cells of any other tissue), (3) prothrombin, the inactive precursor of thrombin, (4) thrombin, the ultimate clotting agent, and (5) calcium ions.

In normal intravascular blood exist fibrinogen, prothrombin, and calcium ions in a state of perfect equilibrium. Upon shedding, this equilibrium is upset by the addition of kinase which is furnished (a) by the lysis of blood cells, mainly platelets, and (b) by the injured cells at the site of the wound. The presence of this additional factor makes possible the conversion of prothrombin to thrombin. The latter then rapidly changes the fibrinogen of the blood to insoluble fibrin which forms the clot. We must discuss briefly a few of the theories which account for the inter-actions of the five factors listed above in the clotting process. We shall ignore the varied nomenclatures which have been used and adhere strictly to that which we have suggested.

Theories: A theory must first account for the conversion of prothrombin to thrombin. All workers agree that calcium and kinase are necessary for this change. Morawitz, Fuld, and Spiro postulated that prothrombin is "activated" to thrombin in the presence of these two factors. No chemical combination between the

three factors was held to occur. Howell believes that calcium alone is necessary for "activation." According to this worker kinase functions by neutralizing a physiological anticoagulant, — "*antiprothrombin,*" associated in plasma with the prothrombin. Pickering emphasizes the rôle of surface contact in the inception of clotting. He believes that this factor releases prothrombin from a protective colloidal complex, and that this freeing of prothrombin is a necessary preliminary to its activation by calcium and kinase.

Opposed to the above "activation" theories is that of Bordet and Delange. These investigators are of the opinion that prothrombin is converted to thrombin by combining chemically with kinase in the presence of calcium ions. A theory of blood clotting must also explain the action of thrombin in bringing about the final stage of clotting. The majority of workers, including all those mentioned above, believe thrombin is an enzyme which has for its specific action the conversion of soluble fibrinogen into insoluble fibrin. Mills and Mathews contend that thrombin reacts quantitatively with fibrinogen to produce fibrin. These same workers suggest that the thrombin mechanism is of only secondary importance in clotting. The most important reaction is the combination of two substances, tissue fibrinogen and blood fibrinogen, in the presence of calcium ions, to give fibrin. The relative merit of the theories can only be judged by a consideration of the nature and properties of the various components of the clotting system.

Fibrinogen: We may define fibrinogen as a substance which, in solution, may be clotted only by thrombin or, of course, by any mixture which will generate thrombin. It is commonly prepared from plasma by "salting out," using either one-half saturation with sodium chloride or one-fifth saturation with ammonium sulphate. As it exists in plasma it is apparently closely connected with prothrombin for several precipitations are usually necessary to separate the two completely. Fibrinogen is a protein of the globulin class. It is coagulable by heat at 56°C. It is almost certainly manufactured in the liver. A solution of fibrinogen serves as an excellent test fluid for thrombin.

Prothrombin: This may be defined as a substance which will clot fibrinogen only in the presence of calcium and kinase. Mellanby has devised the best method of preparing prothrombin. Plasma is diluted ten times with water and adjusted to Ph. 5.3. From the resulting complex isoelectric precipitate, prothrombin is dissolved off by treatment with a very diluted solution of calcium bicarbonate. The prothrombin is then precipitated from the calcium solution by acidification to PH. 5.3. The product when washed with acetone and dried in a vacuum dessicator is a white amorphous powder which is quite stable to heat, being resistant, in solution, to a temperature of 100°C.

We are mainly interested in the conditions governing its activation to thrombin. Calcium ion, while apparently not absolutely necessary for activation (Mellanby), has, however, such a marked accelerating effect on the activation process that its presence is a practical requisite for activation within any significant time. Kinase is admittedly necessary for the conversion of prothrombin to thrombin. The problem to be solved is: "Does kinase 'activate' prothrombin to give thrombin, or do the two generators of thrombin combine quantitatively to yield the active product?" We may summarize briefly the more direct evidence. Bordet and Delange found that the amount of thrombin present in fresh serum obtained by clotting plasma with calcium and kinase depended on the amount of kinase added. Their theory expresses the belief that prothombin and kinase react quantitatively. Mellanby

found that apparently a minimal quantity of kinase was required to produce maximal activation of his prothrombin, and concluded that a quantitative relationship may exist between prothrombin and kinase. But this does not settle the question. As we shall see later, Fischer has prepared a substance which he calls thrombin and which contains lipoid in fairly large amounts. We shall consider the problem more fully as we discuss thrombin. The significant fact which is established by a study of prothrombin is that this originally hypothetical precursor of thrombin is a definite entity present in plasma. So its insertion into any theory of blood clotting is justified.

Thrombin: This may be defined as a substance which will coagulate fibrinogen in the presence of an excess of a soluble oxalate. (The latter, by precipitating calcium ion, eliminates the possibility of the activation of any prothrombin which may be present). John Mellanby has recently prepared a very potent thrombin by the activation of his prothrombin. The moist precipitate obtained by the second isoelectric precipitation, if left standing at room temperature, activates spontaneously, the process requiring about 48 hours. The activated product is no longer precipitable at PH 5.3, but gives an inactive precipitate at PH 5.0 the removal of which purifies the product considerably. The thrombin may then be precipitated from solution by the addition of four volumes of acetone. It is then washed with acetone and dried in the vacuum dessicator, yielding a white powder which is very stable. As prepared by Mellanby, it has a potency such that one gram will coagulate 100,000 c.c.'s of oxalated beef plasma in thirty seconds at 38°C.

In considering the action of thrombin the problem to be settled is whether thrombin is an enzyme or reacts quantitatively to produce fibrin. We shall sum up the evidence. (1) Barratt has shown the relationship between clotting time of fibrinogen and concentration of thrombin to be hyperbolic, that is, the clotting time is inversely proportioned to the concentration of thrombin. The same type of relationship is observed when thrombin concentration is kept constant and the fibrinogen varied. These results indicate that thrombin may be an enzyme. (2) The recovery of thrombin from fibrin by saline extraction has been used as an argument for the chemical combination of thrombin and fibrinogen. Mellanby has shown fairly conclusively that thrombin is merely adsorbed by the fibrin. During the clotting of a fixed amount of fibrinogen solution by thrombin the amount of thrombin removed on the clot depends on the amount originally added. (3) When constant amounts of fibrinogen are clotted by varying amounts of thrombin, the whole of the fibrinogen is transformed to fibrin in every case except when the amount of thrombin added is very small. Under the latter conditions the amount of fibrin separated appears to be related to the amount of thrombin added. But this may easily be explained by supposing that the first formed fibrin adsorbs the greater part of the thrombin present, and the resulting slow action of the residue accompanied by its slow adsorption determines the practical cessation of coagulation. (4) Lastly, we may cite the extreme fragility of thrombin in regard to heat, acid or alkali, and ultra-violet radiation. This fragility is in marked contrast with the stability of prothrombin.

It seems almost certain that thrombin is an enzyme. Its action, as has already been stated, is to change fibrinogen to fibrin. There is some evidence that there is a second phase of thrombin activity, namely, clot resolution. Ruby Hirose in 1934 demonstrated that the clot in contact with its serum undergoes gradual dissolution even under sterile conditions. The products of this action are: (1) a new protein, "fibrinoglobulin," and (2) the original pro-

thrombin. This latent action of thrombin may be of great importance in breaking down clots formed in the body. Thrombin, if injected intravenously, will cause intravascular coagulation. This tends to establish the physiological significance of the substance. The injection of one to three mg. of Mellanby's thrombin killed rabbits in from two to seven minutes. Extensive intravascular clotting was almost invariably observed in the right heart and great veins. Sublethal doses of thrombin cause a decrease in coagulation time which lasts for a very short period, being followed by a marked negative phase (ie. ,very long coagulation time). Immunity to thrombin has not yet been produced by repeated sublethal doses.

We must now consider the chemical nature of thrombin. It is certainly a protein. The question arises as to whether or not it contains kinase which is, as will be seen lipoidal in nature. The evidence presented during the discussion of prothrombin was not convincing in either way. It will be recalled that Mellanby's thrombin contains no phophorus. The work of Albert Fischer leads to the conclusion that thrombin is a calcium-lipoid-protein compound. From a saline extract of minced hen muscle a substance was prepared which possessed marked clotting activity. It could be separated into two fractions, protein and lipoid. Neither of these alone showed any potency, but the two could be combined to yeld an active product. This "muscle thrombin" would coagulate oxalate plasma or pure fibrinogen just as would thrombin prepared by any other method. Apparently muscle thrombin is true thrombin. This work, although it appears to be conclusive, yet has several unsatisfactory aspects. (1) This thrombin is stable in acid solutions. This is certainly not true of thrombin prepared by any other method. (2) No quantitative values are given for the amount of lipoid in the thrombin complex, and (3) no proof is given of the presence of calcium in the complex. Conclusions are very difficult to draw. We must leave the constitution of thrombin for the future to decide. We have shown, however, that thrombin is an enzyme which can clot fibrinogen either in vitro or in vivo. It may further be responsible for the resolution of clots.

Kinase. The significance of a factor derived from the tissues, including the blood cells, in the phenomenon of blood clotting has long been recognized. This factor can eccelorate the spontaneous clotting of blood but can clot fibrinogen only when calcium and prothrombin are also present. Schmidt first obtained such a factor in an alcoholic tissue extract. Bordet and Delange recognized that the active substance was ether soluble but acetone insoluble. They believed it to be a phospholipoid. Howell asserted that the active phospholipoid was cephalin. Gratia, and later Wadsworth and Meltaner showed that cephalin was active while lecithin was quite inactive. Until recently this result was unchanged. However, Fischer and Hecht have prepared extremely pure cephalin and found it to be completely inactive. In the course of their preparation they obtained several active fractions. These invariably contained cholesterol and cerebrosides. However, neither purified cholesterol nor cerebrosides alone or in combination showed any activity. These workers suggest that the active substance may be a complex in which cephalin and cerebrosides are combined in some unknown way. The identity of the lipoid factor in blood clotting is thus another unsettled problem. It early became apparent that there could be obtained from tissues a thromboplastic extract possessing somewhat different properties from the thermostable lipoid. Aqueons or saline extracts were found to be much more active than the isolated lipoid besides being thermolabile. Heating to 70°C. coagulated the active substance in such preparations. Many workers believed this to be mere-

ly the active lipoid in combination with a protein which rendered it extremely soluble. Wooldridge and later Mills worked with such a preparation and gave to it the name "tissue fibrinogen." They believed it combined directly with blood fibrinogen in the presence of calcium to produce insoluble fibrin. Mills investigated the chemical nature of this substance. It behaved like a protein but contained 40% phopholipoid. The two fractions could be separated and each was only slightly active. When recombined the product was very active. It possessed the ability to clot a recalcified plasma from which all the prothrombin had been absorbed by barium sulphate. Such a plasma was not clotted by calcium and cephalin. On the basis of this work Mills advanced his theory of clotting which we have already considered. We see in this work a striking parallel to Fischer's results. It certainly does appear as if the protein involved were prothrombin and the lipoid "kinase." Whether or not the active substance is a true compound of these two constituents or merely a mixture of them cannot be definitely stated.

Anticoagulants. A knowledge of blood anticoagulants is important both practically and theoretically. A very brief review of the means of preventing coagulation will be given. (1) Decalcification has already been discussed. (2) Cooling to within a few degrees of the freezing point delays clotting considerably. (3) The addition of a neutral salt, i.e., sodium chloride, in concentration from 3-7% prevents clotting. Clotting occurs upon dilution. (4) By preventing surface changes, by drawing blood through a paraffined cannula into a paraffined dish clotting is greatly delayed. The importance of surface contact as a factor in clotting should be emphasized. Thrombosis may be produced experimentally by injury to a vessel wall or by introduction of a foreign wettable body into the blood stream. (5) Certain complex organic compounds are good anticoagulants, of which many azo dyes are effective both in vivo and vitro. There is also a group of substances of which germanin, neoarsphenamine, novirudin, liquoid, sulphor-sphenamine are examples. These are effective either in vivo or in vitro. Cysteine is definitely anticoagulant in vitro. Carr and Foote have adduced evidence to show that the hypocoagulability observed in cases of obstructive jaundice is due to the accumulation of cysteine and other nitrogenous end products in the blood. The use of brombenzene effectively reduces the amount of circulating cysteine and reduces the bleeding tendency in experimental animals. (6) Hirudin extracted from heads of leeches is a potent anticoagulant. (7) Lastly we have the concept of physiological anticoagulants. The idea of anticoagulants in the blood being responsible at least partially for its fluidity in vivo has long been held by certain investigators.

There is definitely in normal plasma an anticoagulant which is an antithrombin, i.e., it inhibits the action of thrombin on fibrinogen. This anticoagulant is heat labile. Howell has made a special study of physiological anticoagulants. In 1919 he prepared from dog's liver a substance which possessed market anticoagulant properties and to which he assigned the name heparin. This substance was heat stable. It had no antithrombin activity but was a potent antiprothrombin, i.e., it prevented the clotting of fibrinogen by calcium and kinase and prothrombin. Moreover, when added to plasma it caused the generation in the plasma of a potent antithrombin from a heat labile precursor. This hypothetical substance he called "pro-antithrombin" thereby considerably augmenting the already prevailing confusion in the termnology of coagulation. His further work on the subject has been to improve the methods of preparation of heparin and to show that a substance with the proporties of heparin can be extracted from normal plasma. This

indicates a possible physiological importance. Howell believes "that heparin restores clotting by a double action; by its power to prevent activation of prothrombin to thrombin; and by its power of activating pro-antithrombin to thrombin. Clotting is possible in shed blood since kinase thrombin to anti-thrombin clotting neutralizes heparin."

Recently some work by Mellanby has tended to discredit Howell's conclusions. Mellanby has shown that heparin is a potent antithrombin. However, its action as antithrombin is dependent on the salt concentration of the clotting mixture. With low salt concentration its action is negligible. This was shown by varying the salt concentration of plasma by dialysis, or of fibrinogen solutions by the addition of salt. He has further shown that heparin does not inhibit the activation of prothrombin by calcium and kinase. A mixture of prothrombin + calcium + kinase + heparin after incubation will clot dialyzed plasma very readily, but will not clot normal plasma since in the latter case, due to the presence of salt, the heparin is able to exert its antithrombin effect. Howell, in obtaining his results apparently failed to control the salt concentration of his clotting mixtures However, the significance of Howell's heat labile pro-antithrombin the writer is unable to judge.

In spite of these theoretical differences the fact remains that heparin is a potent and useful anticoagulant both in vitro and in vivo. It has proved useful in operative experiments in which thrombosis was to be avoded. Unfortunately the effect of a single injection of heparin lasts for only a few hours. Continuous infusion is necessary to keep the blood hypocoagulable for any great length of time.

Coagulants. There are many clinical cases in which the need is not for an anticoagulant but rather for a coagulant. I mention only three conditions in which hemorrhage is common, namely, hemophilia, obstructive jaundice, and purpura. Many hemostatics are available from the drug houses for use in such cases. They are mostly tissue extracts. Some are crude lipoidal extracts, and hence supply the "kinase" factor in the clotting system. Others are aqueous or saline tissue extracts and hence presumably contain both prothrombin and kinase. Normal horse serum is very commonly used. It undoubtedly contains kinase. It may possibly also contain some prothrombin or even some thrombin. All these hemostatics are usually of most value when applied directly to the wound. It is probable that in such cases clotting would be accelerated. However, they are occasionally used intravenously, or intramuscularly, or even orally. Their success in these cases is quite unpredictable. Intravenous calcium chloride is commonly used as a means of controlling hemorrhage. There are, however, probably very few cases in which the bleeding tendency is due to a low blood calcium. The most effective hemostatic treatment is the transfusion of normal blood. By this means all the clotting factors are replenished. In the treatment of bleeding in hemophiliacs a very useful method seems to be the induction of mild protein shock. Jones attributes the beneficial effects of this treatment to changes in the blood vessels. The real mechanism is rather obscure. Thrombin would, of course, be the ideal hemostatic. Of course it can be used only externally. It is being widely used in England for local application to wounds.

Conclusions. In conclusion the writer suggests a theory of clotting which is really a composite of several theories. In plasma exists all the elements necessary for clotting. But between these exists a perfect equilibrium and no clotting occurs until this equilibrium is upset by some disturbing factor. It is a well-known fact that bird or fish plasma, if centrifuged completely cell free, is quite stable. By careful technique the same can be demons-

trated for mammalian plasma. Such stable plasma may be coagulated by surface disturbances such as stirring with a feather or diluting with water. These changes probably release prothrombin from a protective complex. Thus the prime requisite for clotting is a change in surface conditions.

In normal clotting of shed blood surface contact has also the effect of causing lysis of cellular elements, the platelets being particularly liable to this effect. This releases both kinase and prothrombin, thus accelerating the clotting of the plasma. It is a noteworthy fact that intravascular clotting can be induced by introduction of foreign wettable bodies into the blood stream, but cannot be induced either by injection of kinase or by complete lysis of platelets in vivo due to injection of saponin. No definite conclusions can be drawn regarding the chemical nature of any of the factors involved in clotting. The mode of action of kinase on prothrombin can not be stated with certainty. It seems certain that thrombin is an enzyme. The action of heparin is still in doubt.

Selected References.

Only a very brief list of references is here published but they will serve as an introduction to the literature in this field.

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For further references apply to the author.

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